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EDITORIAL COMMENT

Triple Antithrombotic Therapy With Prasugrel in the Stented Patient

Concern for More Bleeding*

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There is a large body of evidence, including results of prospective trials, that supports oral anticoagulation therapy (OAT) as the optimal strategy to prevent fibrin-centric thrombotic events (FCTEs). Examples of FCTEs include thromboembolism in patients with mechanical heart valves, deep vein thrombosis, and atrial fibrillation (AF) (1). In a large prospective trial, warfarin was found to be superior to dual antiplatelet therapy (DAPT) with aspirin + clopidogrel in the prevention of vascular events in patients with AF plus 1 or more risk factors for stroke (2). European and American guidelines include a Class I recommendation for lifelong OAT in patients with AF who are at moderate to high risk of thromboembolism (3). It has also been demonstrated in prospective, randomized trials that DAPT with aspirin and a thienopyridine is superior to aspirin + warfarin in the prevention of the platelet-centric thrombotic event (PCTE), stent thrombosis (4). In the European and American Guidelines there is a Class I recommendation to administer uninterrupted DAPT for 1 to 12 months depending on the type of stent used (5,6).

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However, in everyday practice, things are not as cut and dried. Cardiologists regularly encounter patients requiring prophylaxis against *both* events. It is estimated that ~5% of patients undergoing stenting also meet the criteria for OAT (7). It is not surprising that there is a major concern for more bleeding with triple antithrombotic therapy (TAT) with aspirin + clopidogrel + warfarin than DAPT (7). Although TAT is currently recommended for the patient at moderate to high risk of an FCTE undergoing stenting, there are no large-scale prospective data addressing how to best deal with this important clinical conundrum, and the available evidence base to address the efficacy and safety of TAT is limited (5–7). Despite the limited information, specific recommendations based on stent type, clinical setting (acute coronary syndrome [ACS] vs. elective), and hemorrhagic risk have even been given (7). The best prospective evidence of excessive (and unacceptable) bleeding from TAT comes from trials of ACS patients treated with DAPT + a new oral anticoagulant. For example, the addition of apixaban, a factor Xa inhibitor, at a dose shown to be more effective than warfarin in stroke prophylaxis in AF, to aspirin + clopidogrel, was associated with excessive bleeding that resulted in the premature termination of a major ACS trial (8). Greater bleeding was also observed with AF-effective doses of dabigatran in addition to aspirin + clopidogrel versus aspirin + clopidogrel (9). In a recently reported prospective trial, both Thrombolysis In Myocardial Infarction (TIMI) bleeding and all-cause mortality were ~60% higher in stented patients treated with TAT with clopidogrel versus clopidogrel + warfarin (10).

Where else is the evidence not so cut and dried? Controversy exists in the area of personalized antiplatelet therapy. Despite the overwhelming evidence of a slow, weak, and unpredictable pharmacodynamic effect, clopidogrel remains the most widely used $P2Y_{12}$ inhibitor in the patient undergoing stenting. Moreover, a substantial proportion of clopidogrel-treated patients have on-treatment high platelet reactivity (HPR) to adenosine diphosphate. Based on a large body of observational evidence, HPR has been identified as a risk factor for post-percutaneous coronary intervention ischemic event occurrence, including stent thrombosis (11). However, the relationship of HPR to ischemic risk has never been studied in patients on TAT. Furthermore, 3 prospective trials of personalized antiplatelet therapy failed to demonstrate the utility of adjusting $P2Y_{12}$ inhibitor therapy based on platelet function testing. In addition, the safety and efficacy of the new $P2Y_{12}$ inhibitors have never been assessed in combination with OAT (12–14). In the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38) study, patients were excluded from enrollment if they were receiving OAT that could not be safely discontinued. If OAT was indicated, a blinded study drug was discontinued, and open-label thienopyridine use was left to the discretion of the treating physician (15). Finally, in the boxed warning addressing "bleeding risk" contained in the prescribing information for prasugrel, caution was given regarding the concomitant use of medications that increase the risk of bleeding (e.g., warfarin) (16).

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In this issue of the *Journal*, Sarafoff et al. (17) report their experience in 377 consecutive patients who underwent successful stenting and platelet function testing and were discharged with a 6-month regimen of TAT. Among these patients, 21 were treated with prasugrel instead of clopidogrel. HPR determined by impedance aggregometry was the indication for prasugrel in the majority (86%). The indication for OAT in the clopidogrel group was largely atrial fibrillation (80%), whereas the indication in the prasugrel group was left ventricular thrombus (33%), atrial fibrillation (29%), and pulmonary embolism/deep vein thrombosis (19%). Even though the study was not powered to assess clinical endpoints, prasugrel therapy was associated with a disturbing nearly 5-fold greater TIMI major bleeding than clopidogrel therapy. The information on where the bleeding occurred is limited except that 1 intracranial hemorrhage was reported in the prasugrel group. Despite the lower on-treatment platelet reactivity in the prasugrel group, no significant difference in the combined ischemic endpoint occurrence was observed (17). The variable and greater on-clopidogrel platelet reactivity observed by the authors is consistent with previous reports from the same group, and the successful effect of prasugrel in overcoming HPR is similar to that reported by others (18,19). The current study supports the data obtained in the absence of OAT from the TRITON trial that demonstrated greater bleeding with prasugrel compared with clopidogrel (15). In the current study, the coadministration of OAT with prasugrel appeared to exaggerate this difference.

The authors should be recognized for their exploration into the uncharted territory of TAT with prasugrel. The primary indication for prasugrel use in their study was HPR on clopidogrel therapy. However, at this time, we do not have large-scale prospective data demonstrating that personalizing antiplatelet therapy is effective and safe in stented patients whether or not they are receiving OAT. Preliminary data from the same authors and others suggest that there may be a therapeutic window for $P2Y_{12}$ inhibitors in stented patients not receiving OAT (11,18). Further work should be done to explore this concept in those receiving TAT. Two scenarios are possible: 1) The therapeutic window of platelet reactivity may not be the same in the presence of OAT. Bleeding risk may be reduced by avoiding overinhibition and titrating the $P2Y_{12}$ inhibitor into the upper therapeutic range of on-treatment platelet reactivity. In the current study, low on-treatment platelet reactivity in the prasugrel-treated patients may have contributed to the observed excessive bleeding. 2) The intensity of anticoagulant effect needed for optimal prevention of FCTE may be lower in the presence of $P2Y_{12}$ inhibition.

We know that the $P2Y_{12}$ receptor plays a central role in post–stent thrombotic event occurrence, and its inhibition cannot be substituted by anticoagulation (4). Similarly, in patients at moderate to high risk of FCTE occurrence, $P2Y_{12}$ inhibition cannot substitute for OAT (4). Balancing the intensity of the 2 therapies is a delicate act. In the future, the balancing act may be facilitated by a laboratory method that can assess both coagulation and platelet reactivity in these bleeding- and thrombosis-prone patients. We agree with the authors' conclusion that a substantial amount of work is necessary before we coadminister OAT with a potent $P2Y_{12}$ inhibitor such as prasugrel.

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REFERENCES

1. Guyatt GH, Akl EA, Crowther M, et al. American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:7S–47S.
2. Connolly SJ, Pogue J, Hart RG, et al., ACTIVE Investigators, Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066–78.
3. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 2006;48:854–906.
4. Rubboli A, Milandri M, Castelvetri C, Cosmi B. Meta-analysis of trials comparing oral anticoagulation and aspirin versus dual antiplatelet therapy after coronary stenting. Clues for the management of patients with an indication for long-term anticoagulation undergoing coronary stenting. Cardiology 2005;104:101–6.
5. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44–122.
6. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.
7. Lip GY, Huber K, Andreotti F, et al. Consensus Document of European Society of Cardiology Working Group on Thrombosis. Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting. Eur Heart J 2010;31:1311–8.
8. Alexander JH, Lopes RD, James S, et al., APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 2011;365:699–708.
9. Oldgren J, Budaj A, Granger CB, et al., RE-DEEM Investigators. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J 2011;32:2781–9.
10. Dewilde W, Oirbans T, Verheugt F, et al. The WOEST trial: first randomized trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting. Paper presented at European Society of Cardiology, Hotline III; Munich; August 28, 2012.
11. Gurbel PA, Tantry US. Do platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents?: Platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents. Circulation 2012;125:1276–87.
12. Price MJ, Berger PB, Teirstein PS, et al., GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA 2011;305:1097–105.
13. Trenk D, Stone GW, Gawaz M, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopi-

dogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. J Am Coll Cardiol 2012;59:2159–64.
14. Collet JP, Cuisset T, Rangé G, et al., ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012;367:2100–9.
15. Wiviott SD, Braunwald E, McCabe CH, et al., TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
16. EFFIENT (prasugrel) tablets prescribing information. Available at: http://pi.lilly.com/us/effient.pdf. Accessed on January 29, 2013.
17. Sarafoff N, Martischnig A, Wealer J, et al. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. J Am Coll Cardiol 2013;61:2060–6.
18. Sibbing D, Steinhubl SR, Schulz S, et al. Platelet aggregation and its association with stent thrombosis and bleeding in clopidogrel-treated patients: initial evidence of a therapeutic window. J Am Coll Cardiol 2010;56:317–8.
19. Alexopoulos D, Dimitropoulos G, Davlouros P, et al. Prasugrel overcomes high on-clopidogrel platelet reactivity post-stenting more effectively than high-dose (150-mg) clopidogrel: the importance of CYP2C19*2 genotyping. J Am Coll Cardiol Intv 2011;4:403–10.

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